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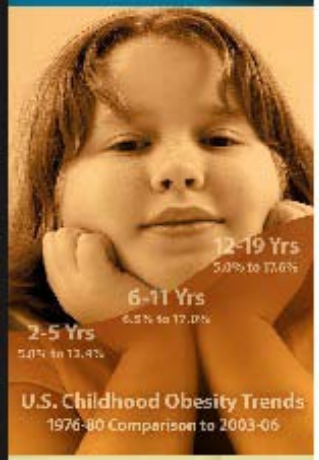

NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity

Research Strategies and Key Data Needs (Group B)

Morris White (chair)
Abee Boyles (rapporteur)

Crabtree Marriott Hotel
January 11-13, 20111

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

Research Strategy/Data Needs (Group B) Members

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Terry Davidson, Purdue U	Angel Nadal, Miguel Hernandez U
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Keith Houck, US EPA	Ellen Silbergeld, John Hopkins U
Duk-Hee Lee, Kyungpook National University School of Medicine	Christina Teng, NIH/NIEHS/NTP
Juliette Legler, Vrije University Amsterdam	Morris White, Harvard (chair)

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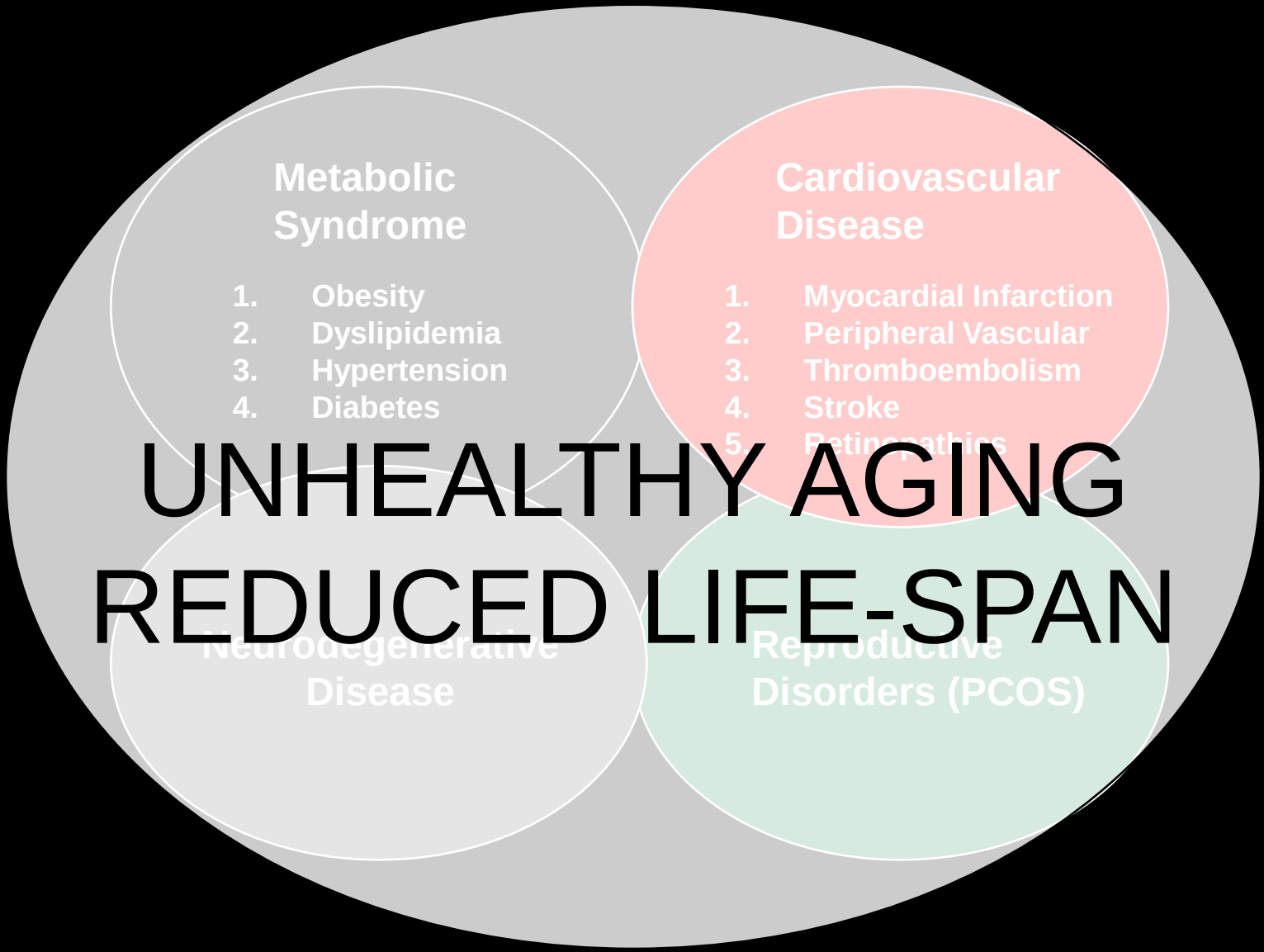
COMMON PATHOLOGY ASSOCIATED WITH INSULIN RESISTANCE



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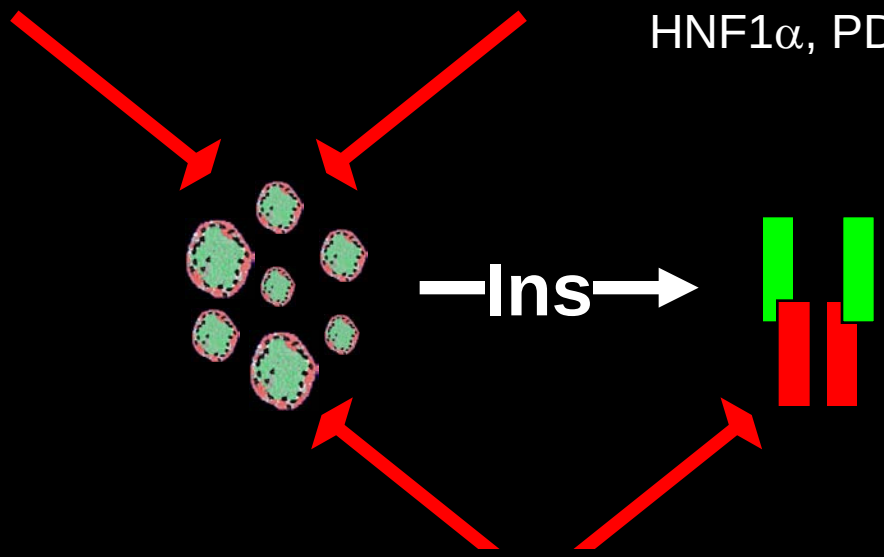
PATHWAYS TO DIABETES

Catastrophic
Destruction
(autoimmune)

T1DM

MODY

Monogenic
Dysregulation
(HNF4α, GK,
HNF1α, PDX1, HNF1β)



T2DM

Metabolic
Inflammation and
Nutrient Excess
CNS Input
Pregnancy

Are there immediate data gaps that if filled would provide significant direction to longer term research programs?

- Fill in the gaps in screening the effect of toxins upon insulin signal transduction cascades using rapid HTS and physiologically relevant secondary screens
- Establish how toxins modulate inflammatory pathways that might modulate insulin signaling and its regulators
- Establish whether a toxin modulate ER stress (liver)
- Establish whether toxins modulate mitochondrial function, shape, ETC function/coupling, ATP production

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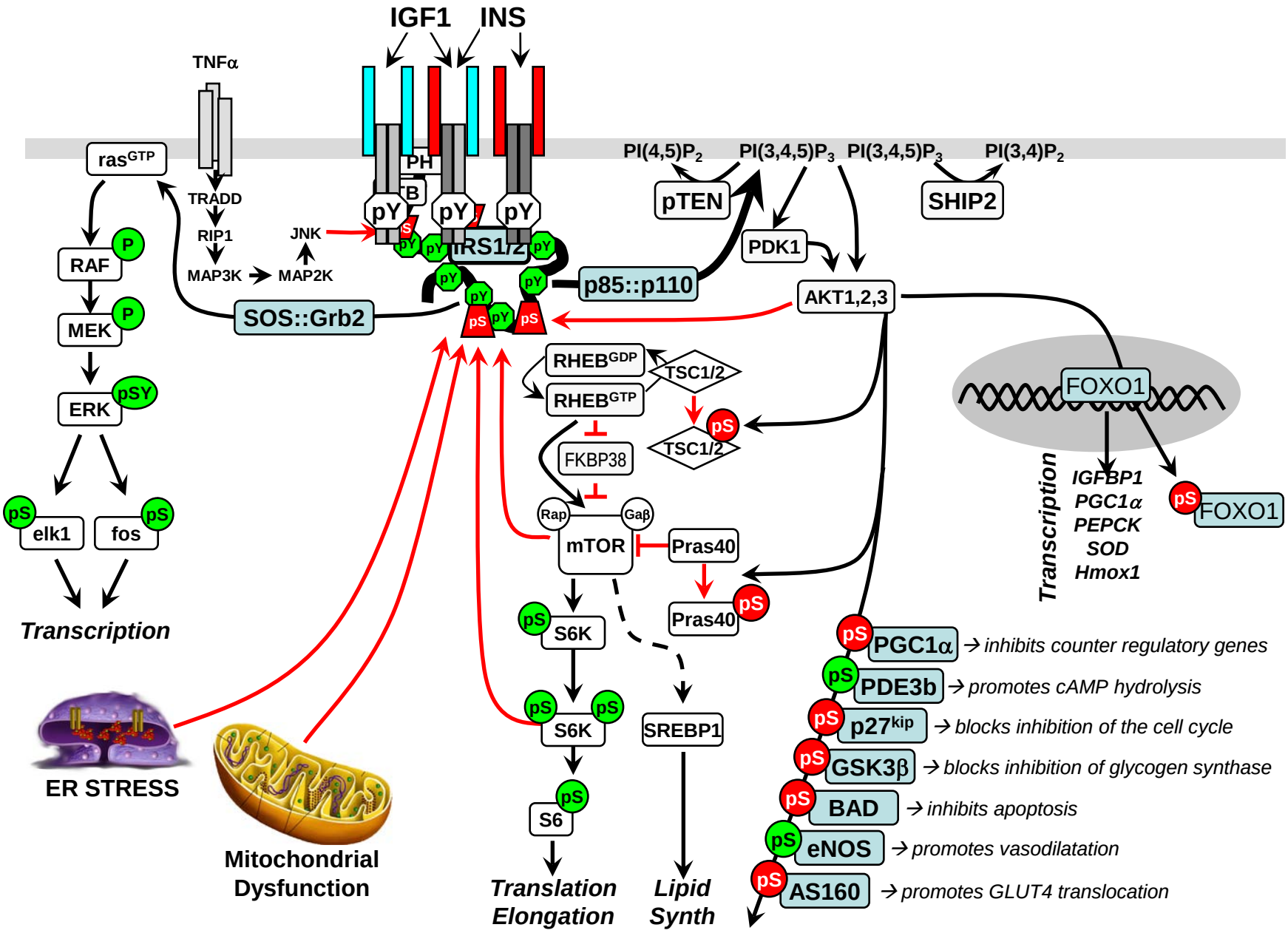
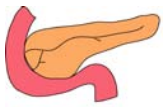
A MECHANISM OF INSULIN SIGNALING



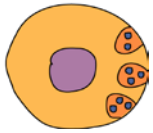
Are there immediate data gaps that if filled would provide significant direction to longer term research programs?

- Fully develop new NTP resources and bioinformatic tools
  - e.g., DrugMatrix, NextBio, CoPub, CoPub+DrugMatrix
  - Validate CoPub and determine whether CoPub can be combined with DrugMatrix or Next Bio
- Develop strategies to validate Tox21 findings by extending analysis into physiologically relevant secondary screens
  - Overcome methodological limitations for the use of physiological relevant cells in HTS.
  - Employ humans cells/stem cells/islets or other accessible human cells.
  - Use physiologically relevant animal (rodent/primate) cells important to diabetes: islet, muscle, hypothalamus, stem cells

High-throughput screening for small molecular compounds that increase IRS2 mRNA expression in human beta-cells

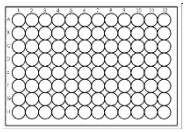


Human Islets



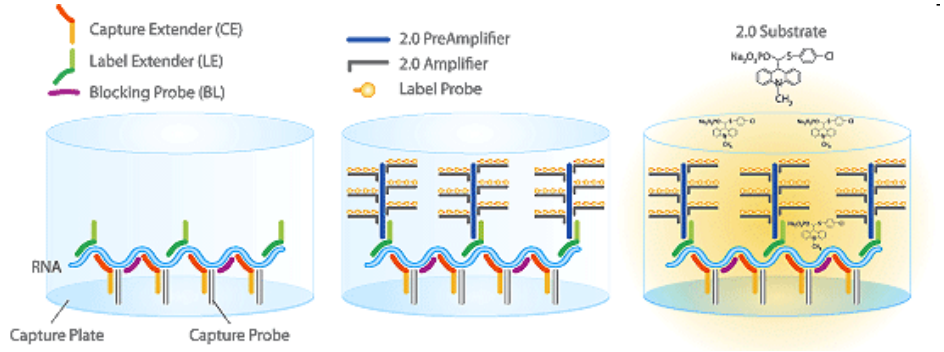
Fasted O/N

+ compounds



4 hours

Lyse



Panomics Quanti-Gene 2.0 kit (RNA expression analysis)

3120 compounds tested (twice in the Primary screen and three times in the Secondary)

↓

About 100 compounds found to be positive

↓

11 compounds were chosen for testing in animal models considering toxicity information

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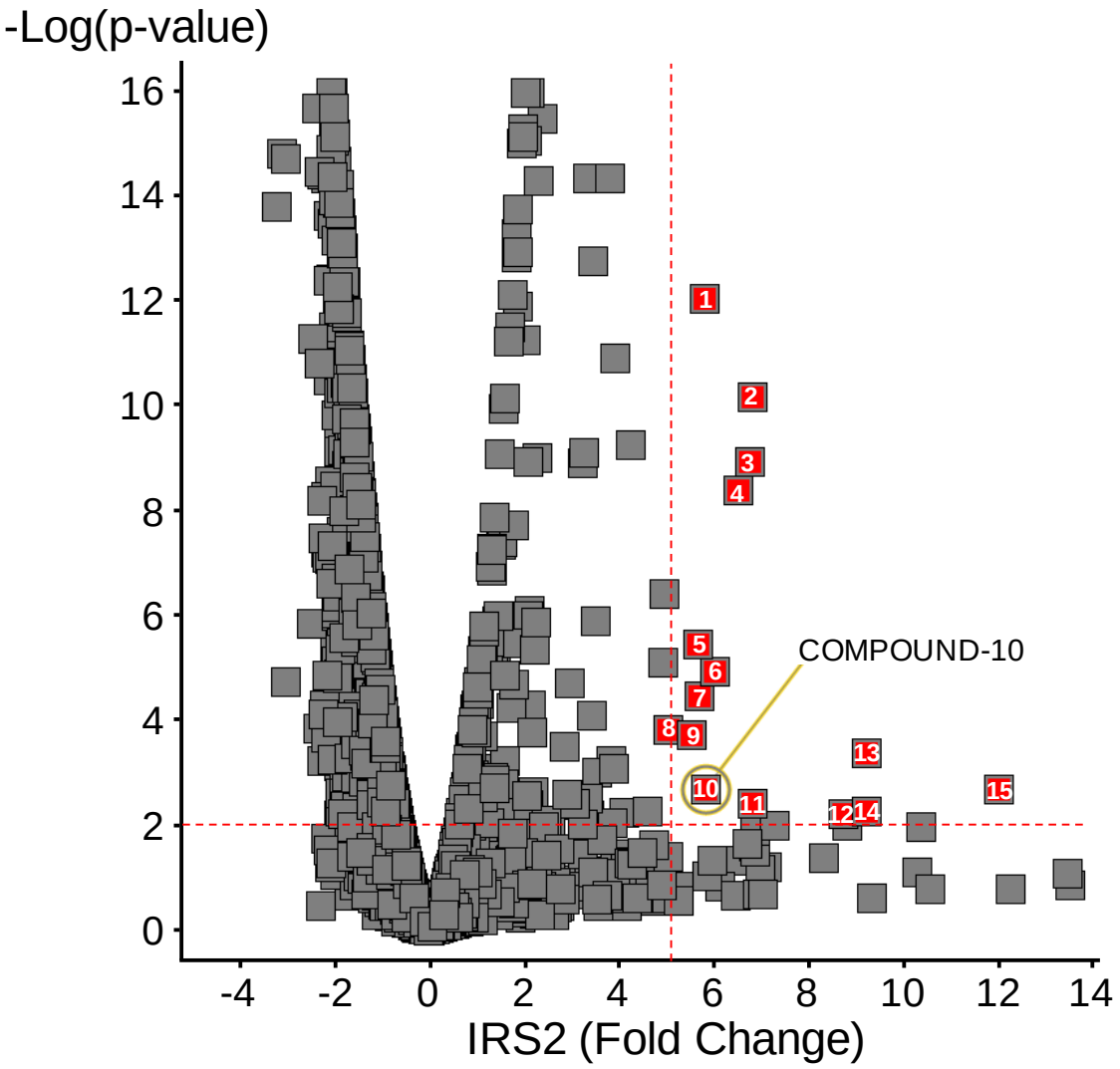
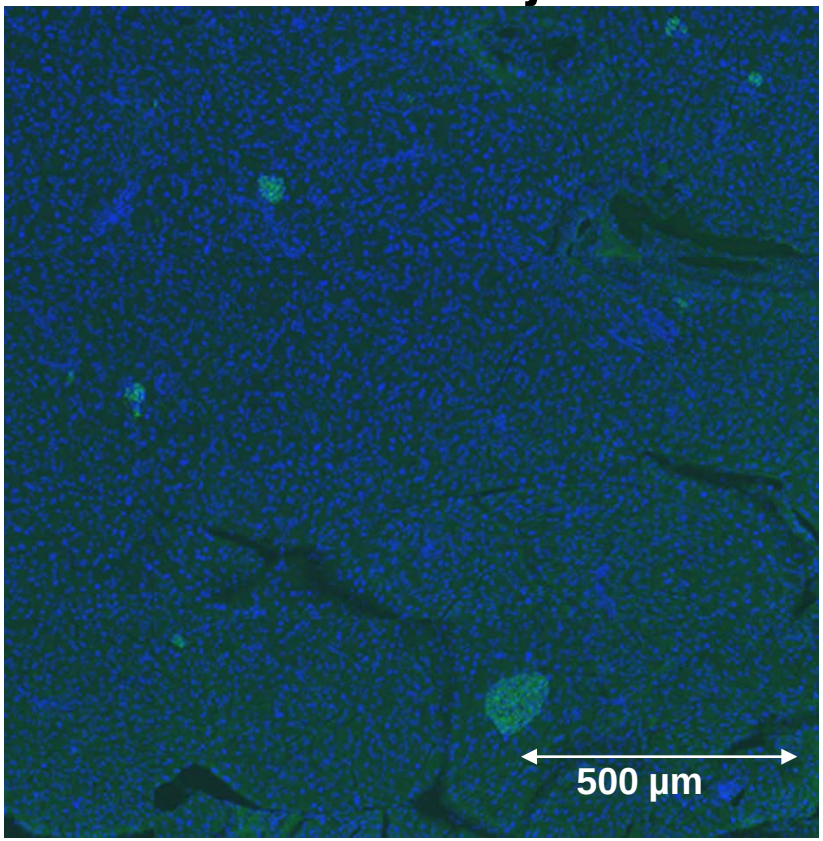
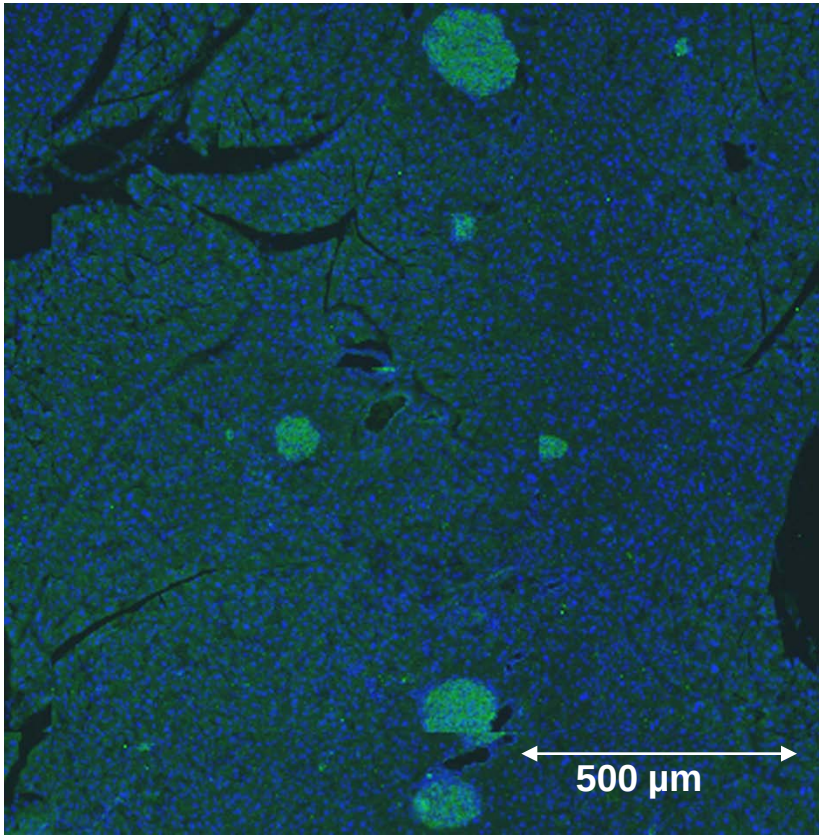
CHEMICAL SCREENING OF HUMAN ISLETS FOR INDUCERS OF IRS2 EXPRESSION



3 weeks of once a day injections → **Analysis of ß-cell mass**



Vehicle



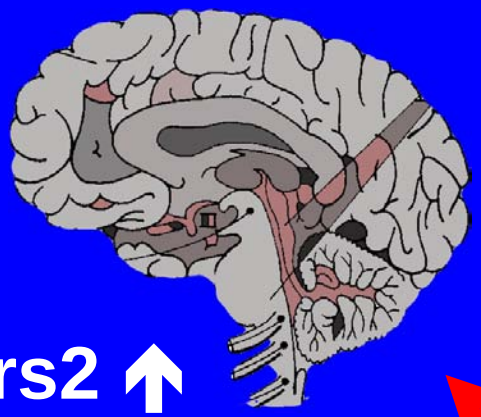
CMPD-10

Insulin immunostaining of representative pancreas sections from 9-week-old C57BL/6 mice treated with one of compounds or vehicle for 3 weeks.

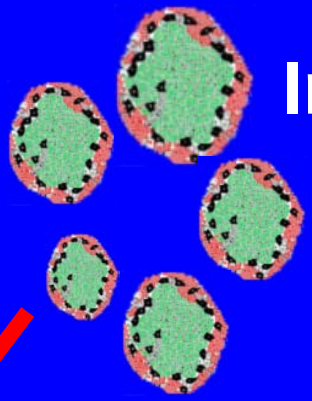
Other Research Needs and Challenges

- Investigate the relation of nutraceuticals (vitamin D, omega 3, etc) to signaling cascades
- Design ways to investigate whether toxins disrupt tissue/organ crosstalk (Brain•β-cell•liver)
- Integrate toxin metabolism/tissue distribution with other HTP data
- Recognize that T1D and T2D have some common factors (beta cell failure)

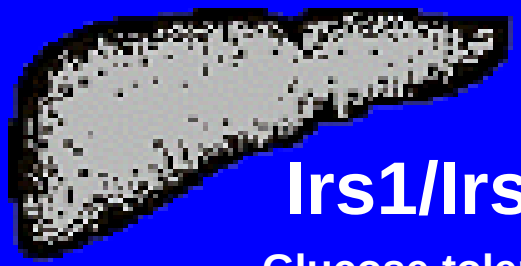
IRS-PROTEINS INTEGRATE CENTRAL AND PERIPHERAL NUTRIENT HOMEOSTASIS



Irs2 ↑
Body weight ↓
Lifespan ↓



Irs2 ↑
β–cell growth ↑
β-cell function ↑
β-cell survival ↑



Irs1/Irs2 ↑
Glucose tolerance ↑

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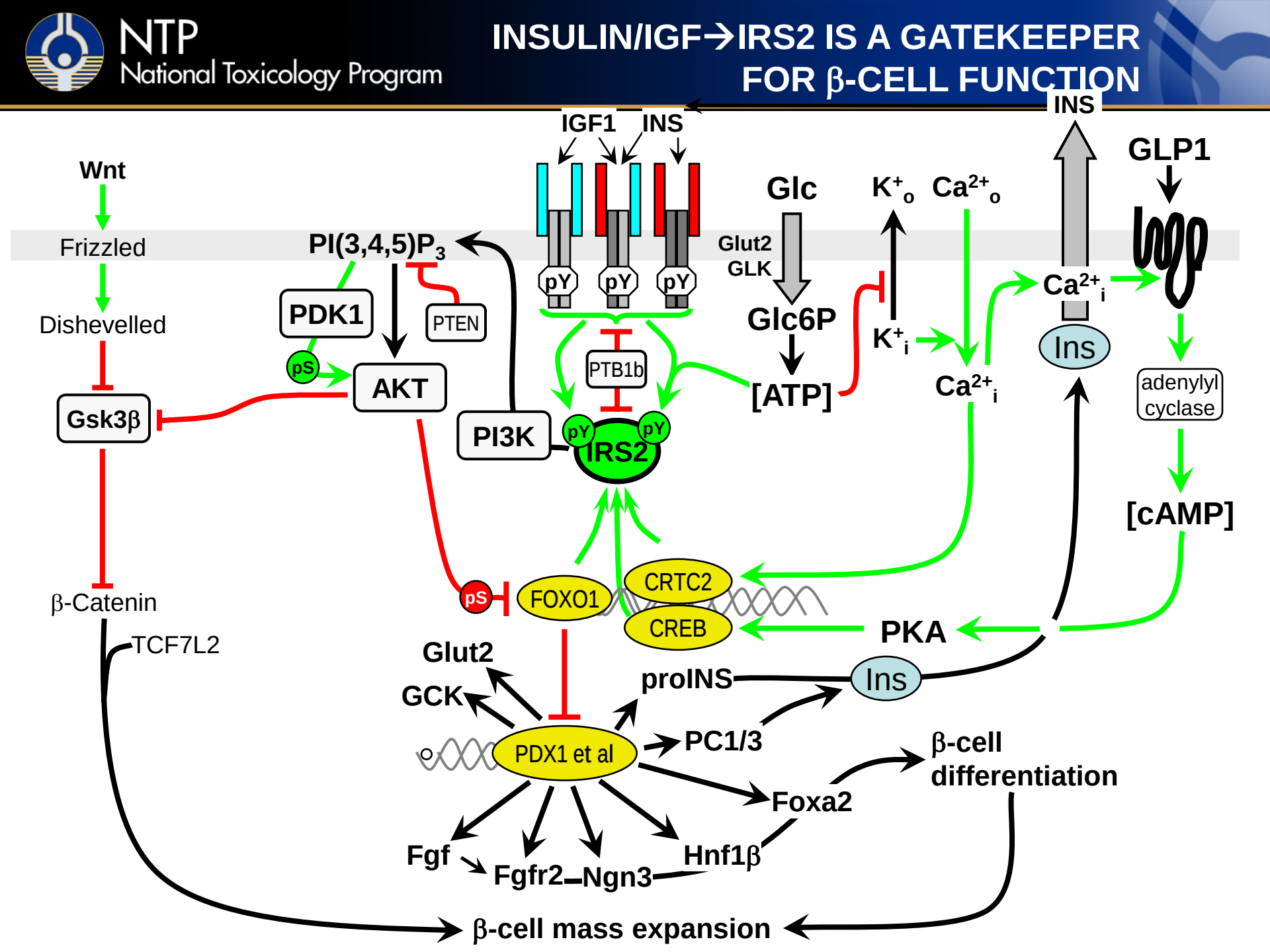
INSULIN/IGF→IRS2 IS A GATEKEEPER FOR β-CELL FUNCTION



Focus on β-cells!

- Not many of them.
- Glucose oxidation/mitochondrial function is critical for function.
- Growth, survival and loss of β-cells is important for glucose homeostasis
- Most GWAS hits for diabetes (type 1 and 2) identify β-cell genes.